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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/753,851	12/02/96	WEINBERG J	1579-21

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MARY J WILSON
NIXON AND VANDERHYE
8TH FLOOR
1100 NORTH GLEBE ROAD
ARLINGTON VA 22201-4714

EXAMINER	
DIBRINO,M	
ART UNIT	PAPER NUMBER
1644	60

DATE MAILED: 09/12/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
WEW 3096	08/753851
Examiner	**Group Art Unit**
GAMBEL	1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 3/14/00; 6/12/00.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 9-12, 14-19, 23-25 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☑ Claim(s) 9-12, 14-19, 23-25 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s)._____

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other_____

Office Action Summary

DETAILED ACTION

1. A request for continued examination under 37 CAR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CAR 1.114, and the fee set forth in 37 CAR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CAR 1.114. Applicant's submission filed on 6/12/00 (Paper No. 59) has been entered.

Applicant's previously unentered amendment, filed 3/14/00 (Paper No. 57), is acknowledged. Claims 8 was canceled. Claims 1-7, 13, 21-22 have been canceled previously Claims 9, 11, 12 and 16 have been amended.

Claims 9-12 and 14-19 and 23-25 are pending.

Claim 20 was not entered.

2. The text of those sections of Title 35 USC not included in this Action can be found in prior Actions. The rejections of record can be found in previous Office Actions (Paper Nos.16/22/34/38/41/46/50/55/58).

As pointed out previously that the instant claims are free of the prior art, this Office Action will be considering both previously elected and nonelected species encompassing anti-CD44 antibodies, soluble CD44, CD44 oligopeptides and hyaluronate

Therefore, claims 8-12, 14-19 and 21-25 are under consideration.

3. Applicant's submission, filed 2/3/00 (Paper No. 54) has placed this application in compliance with the Sequence Rules.

4. Formal drawings and photographs have been submitted which fail to comply with 37 CAR 1.84. Please see the form PTO-948 previously sent in Paper No. 26.
Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes.

6. Claims 9-12 and 14-19 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention essentially for the reasons of record set forth in Paper Nos. 46/50/55/58.

Applicant's arguments, in conjunction with the Weinhold declaration under 37 C.F.R. § 1.132, filed 3/14/00 (Paper Nos. 56/57), have been fully considered but are not found convincing.

Applicant argues in conjunction with Weinhold that the ability of blocking HIV infection of mononuclear phagocytes using CD44 blocking agents is of obvious significance; given the importance of mononuclear phagocytes and monocytotropic stains of HIV in the transmission and spread of HIV infection. Applicant asserts that strategies that use anti-CD44 treatments would therefore target these critically important cell types.

It appears that Section 5 of the Weinhold Declaration indicate that results obtained in vivo and described in this application would give little reason to doubt the effectiveness of the claimed approach.

However, the only Example disclosed in the specification as-filed relies upon in vitro infection studies. Therefore, it is not clear what in vivo studies applicant is relying upon.

While Weinhold relies upon the successful use of antibodies and soluble receptors in the treatment of inflammatory diseases such as arthritis and inflammatory bowel disease; such studies do not necessarily correlate with inhibiting CD44-facilitated HIV infection as it reads on in vivo therapy of treating HIV infections, as encompassed by the claimed methods. Applicant's reliance upon other therapeutic methods rely upon pathological conditions that differ in etiologies and, in turn, rely upon different ingredients, process steps and therapeutic endpoints than that encompassed by the claimed methods.

While anti-CD44 antibodies may have been able to reduce inflammation in mice, which relies upon inhibiting leukocyte adherence; the instant claims encompass inhibiting HIV infection. The nature as the mechanisms of action of the disease states or conditions differ.

In contrast to applicant's assertions, the skilled artisan as well as the rejection of record were well aware of the lack of correlation or predictability between in vitro and animal models and methods of reducing or inhibiting HIV infection, particularly in vivo at the time the invention was made.

In contrast to applicant's assertions or record;t he examiner does not require 100% efficacy to meet the 112, first paragraph, enablement requirements. Rather, it has been noted that both the examiner and the applicant have agreed that the instant application has demonstrated the ability of CD44-specific antibodies to inhibit HIV infection of mononuclear phagocytes in vitro under defined conditions. However, the examiner and the applicant have disagreed whether this would be predictive of the ability of CD44-specific antibodies to inhibit HIV infection of any susceptible cell in vitro and in vivo, encompassed by the claimed methods. The rejection of record has not been based upon an issue of 100% effectiveness, as argued by applicant.

In contrast to applicant's reliance on Ueno et al. (U.S. Patent No. 4,840,941) to support the instant methods; the following of record is noted. While there may some evidence that CD44-specific agents including CD44-specific antibodies/peptides and hyaluronic acid/hyaluronate can inhibit HIV infection and expression under in vitro conditions; there is insufficient evidence that the mechanism of action operates via CD4-facilitated entry of HIV into cells. For example, Ueno et al. (U.S. Patent No. 4,840,941) discloses the criticality of sulfate groups in the inhibition of HIV infectivity and reverse transcriptase activity (see entire document, particularly Example 9).

With respect to the lack of consistency between applicant's assertions of record and observations; the following is reiterated in response to applicant's arguments and reliance of record on targeting CD44 on monocytes to reduce or prevent HIV infection, as encompassed by the claimed methods.

It has been well known in the art that cellular CD4 has been recognized as the predominant membrane protein that interacts with HIV. However, it has been well known that HIV infection occurs in cells that express variable or no detectable levels of CD4. It has been well known that $CD4^+$ T cells are the primary target of HIV infection both in vitro and in vivo. Therefore, it would not have been predictable that targeting CD44 in mononuclear phagocytes would affect HIV infection of any susceptible cell either in vitro or in vivo. For example, either the individual or the blood would be infected by HIV via CD4, irregardless of blocking CD44 infectivity of mononuclear phagocytes. Further, it is noted that CD44-specific antibodies can block HIV infection of mononuclear phagocytes in vitro, however these same antibodies can not block the infection of mitogen-stimulated lymphocytes or cells of a T lymphocyte line in vitro (Rivadeneira et al., Aids Research and Human Retroviruses, 1995; see entire document including Abstract; of record). Therefore applicant's assertions of record have not appeared consistent with applicant's own observations

Applicant has not disclosed how to use CD44-specific antibodies, soluble CD44, CD44 oligopeptides and hyaluronate to inhibit HIV infection or to inhibit CD44-facilitated HIV infection therapeutically in humans. There is insufficient information or nexus of the invention with respect to the in vitro or in vivo ability of claimed therapeutic strategies to inhibit HIV infection or to inhibit CD44-facilitated entry of HIV into cells in vivo or into monocytic cells in vitro in a mixed cell population. In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs such as antibodies can be species- and model-dependent, it is not clear that reliance on the in vitro inhibition of monocyte infection by a particular HIV strain (Example on page 31 of the instant specification) accurately reflects the relative efficacy of the claimed therapeutic strategies, which broadly encompass preventing or treating HIV infection, as disclosed in the specification and commensurate in scope with the claimed invention. In the absence of objective evidence commensurate in scope with the claimed methods, applicant has not provided convincing objective evidence that the claimed invention is effective as a therapeutic or preventative for HIV infection based on the in vitro inhibition of HIV infection of monocytes in vitro alone.

It has been well known in the art that retroviral infections in general, and HIV infections in particular, are refractory to anti-viral therapies. The obstacles to therapy of HIV are well documented in the literature. These obstacles include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed invention with a reasonable expectation of success and without undue experimentation.

Further, it has been well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion. Further, as taught by Fahey et al. (Clin. Exp. Immunol. 88: 1-5, 1991; 892, of record), clinical trials using a variety of immunologically based therapies have not yielded successful results in the treatment and/or prevention of HIV infection (see Table 1). Fahey et al. also disclose in vitro-in vivo discrepancy involved in applying Receptor-Directed Treatments involving CD4-specific inhibitors (see page 3, column 1). Fahey et al. discloses that monoclonal antibody therapies have not provided any clinical benefits and "it is not clear how adding these additional antibodies would make a difference" (see page 3, second column, third full paragraph).

In support, Daar et al. (PNAS 87: 6574-6578, 1990) discloses high concentrations of soluble CD4 required for neutralizing infection poses a formidable problem for such treatment of HIV-1 infection in vivo (see entire document including Abstract and Discussion).

Haynes et al. (Science 271: 324-328, 1996) also teaches the limitations of protective immunity to HIV infection, including that "Current animal models of either HIV or simian immunodeficiency virus (SIV) fall short of precisely mirroring human HIV infection" and that "lacking these models, researchers must turn towards human clinical trials to answer many of the difficult questions about HIV pathogenesis and HIV vaccine development" (see page 40, column one, third paragraph).

Fox (Biotechnology 12: 128, 1994) also discloses that ability to treat and/or prevent HIV infection is highly unpredictable and has met with very little success.

Sommerfelt et al. (J. Gen. Virol. 76: 1345-1352, 1995) discloses that certain antibodies directed against CD18, CD11b and CD11c inhibited HIV-1 induced syncytium formation but not entry (Abstract). Also, certain anti-ICAM-3 antibodies inhibited HIV-1 specific entry but not syncytium formation and only one antibody inhibited HIV-1 induced syncytium formation , entry and infectivity under in vitro conditions (Abstract and Results). Here, it is noted that inhibition was not complete under in vitro conditions using cell lines. Also, Sommerfelt et al. disclose that the inhibitory anti-adhesion antibodies varied on the cell type tested as well as the type of assay (see Results and Discussion). This reference also discloses that cells which lack certain adhesion molecules are still susceptible to HIV-mediated fusion and that HIV-1 has the capacity to exploit different cell surface molecules to different cell types in order to achieve membrane fusion and entry (see Discussion, particularly page 1351, paragraph 1). While certain adhesion molecules may play a role as a coreceptor of HIV-1 or the infection or spread of HIV-1 ; CD44--specific inhibitors appear limited in their ability to their ability to suppress infection, as encompassed by the claimed methods which involve in vivo administration including treating infected individuals.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective methods to suppress the infection of leukocytes with HIV wherein said method comprises administering to a subject exposed to or infected by HIV, including the use of adhesion-based reagents, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for suppressing HIV infection in vivo.

As pointed out previously; applicant's arguments of record have not been found persuasive and the rejection is maintained.

It has been noted that if applicant limits claims to the in vitro inhibition of HIV infection of mononuclear phagocytes or monocytes, then the rejection under 35 U.S.C. § 112, first paragraph would be withdrawn.

7. Claims 13-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "The disclosed and claimed agents (anti-CD44 antibodies, soluble CD44, CD44 oligopeptides and hyaluronate) to inhibit HIV infection of mononuclear phagocytes (versus a mixed cell population) in vitro; does not reasonably provide enablement for any "agent that binds CD44. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies "agents that bind CD44" other than those encompassed by "anti-CD44 antibodies, soluble CD44, CD44 oligopeptides and hyaluronate".

An alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property (e.g. structural or functional). Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use of the claimed ligands in manner reasonably correlated with the scope of the claims to stimulate T cells response to transfected tumor cells.

Further, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. Minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Therefore, structurally unrelated compounds encompassed by the claimed "agents that bind CD44" would be expected to have greater differences in their activities.

Here applicant has not provided the defining structural or correlative teachings sufficient to enable one of skill to isolate and identify the "agents" with the appropriate structural characteristic or property of the instant "agents" to the extent that one of skill would be able to predictably identify the claimed "ligands". It is noted that the known anti-CD44 agents indicated herein differ with respect to structure to the extent that the skilled artisan would not envision one in view of the other. Even those these ligands have overlapping functional properties, these ligands differ with respect to structure and function.

Since the disclosure fails to describe the common structural attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of a limited number of ligands and the ability to screen, is insufficient to enable the genus, encompassed by the claimed invention.

The problem of predicting protein structure from such limited information of a limited number of known ligands protein and, in turn, utilizing predicted structural determinations to ascertain functional aspects of other ligands, including unknown ligands and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

In addition, the issues concerning the lack of predictability of inhibiting HIV with different reagents as well as with different anti-adhesion molecule agents are addressed above in Section 6.

Insufficient direction or guidance is provided to assist one skilled in the art in the selection of any "anti-CD44 agent" other than those disclosed in the specification as filed nor is there evidence provided that other such "anti-CD44 agent" can inhibit HIV infection of monocytes in vitro. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, making and using "anti-CD44 agents that inhibit HIV infection of mononuclear cells would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicant's arguments are not found persuasive.

8. The previous rejection under 35 U.S.C. § 112, first and second paragraphs, with respect to the recitation of "compounds, different from said anti-CD44 antibody, that blocks receptors for HIV infection on said mononuclear phagocyte" has been obviated by the cancellation of these claims.

9. Upon reconsideration of applicant's amended claims, filed 5/14/00 (Paper No. 57); the previous rejections of claim 11 under 35 USC 112, first and second paragraph, for satisfying the biological deposit of the A1G3 antibody/hybridoma and providing the ATCC Accession Number for this antibody/hybridoma are withdrawn.

10. Upon reconsideration of applicant's amended claims, filed 5/14/00 (Paper No. 57); the previous rejections under 35 U.S.C. § 102(b) as being anticipated by Ueno et al. (U.S. Patent No. 4,840,941)under 35 U.S.C. § 103 as being unpatentable over Ueno et al. (U.S. Patent No. 4,840,941) in view of the art known use of AZT (zivodudine) to treat HIV infections at the time the invention was made have been withdrawn.

11. No claim is allowed.

It has been noted that claims drawn to methods of inhibiting HIV infection of mononuclear phagocytes (versus a mixed cell population) in vitro with CD44-specific antibodies would be considered allowable.

As indicated previously, it has been noted that applicant has clearly stated that the instant invention is not drawn to the use of CD44-specific immunotoxins and that the current claimed recitation supports this conclusion.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

PHILLIP GAMBEL

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
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